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The role of esmolol in sepsis: a meta-analysis based on randomized controlled trials

Ya Wei[1†], Fengshan Bo[2†], Jiakai Wang[1], Jianyu Fu[1], Yuyang Qiu[3], Hongying Bi[1], Dehua He[1] and Xu Liu[1*]

Abstract

Background Sepsis is associated with a high incidence and mortality and poses a significant challenge to the treatment. Although esmolol has shown promise in sepsis treatment, its efficacy and safety remain contentious. This meta-analysis aims to clarify the role of esmolol in sepsis management.

Methods PubMed, Embase, Web of Science, Cochrane library, clinicaltrials.gov and the Chinese Clinical Trial Registry were searched and references of relevant reviews and meta-analysis were also screened for appropriate studies. Keywords and free words of 'sepsis', 'esmolol' and 'randomized controlled trials' were used for search. Meta-analysis was performed using RevMan 5.3 software.

Results Fifteen studies involving 1100 patients were included. Compared with the control group, patients receiving esmolol exhibited significantly decreased 28-day mortality (RR, 0.69; 95% CI, 0.60 to 0.81; $P<0.0001$), heart rate (HR) (SMD, -1.15; 95% CI, -1.34 to -0.96; $P<0.0001$), cardiac troponin I levels (cTnI) (SMD, -0.88; 95% CI, -1.13 to -0.64; $P<0.0001$), length of intensive care unit (ICU) stay (SMD, -0.46; 95% CI, -0.62 to -0.3; $P<0.0001$) and duration of mechanical ventilation (SMD, -0.28; 95% CI, -0.48 to -0.09; $P=0.004$) and significantly increased central venous oxygen saturation ($ScvO_2$) (SMD, 0.66; 95% CI, 0.44 to 0.88; $P<0.0001$).While, esmolol had no significant influence on norepinephrine dosage (SMD, 0.08; 95% CI, -0.13 to 0.29; $P=0.46$), mean arterial pressure (MAP) (SMD, 0.17; 95% CI, -0.07 to 0.4; $P=0.16$), central venous pressure (CVP) (SMD, 0.16; 95% CI, -0.04 to 0.35; $P=0.11$) and left ventricular ejection fraction (LVEF) (SMD, 0.21; 95% CI, -2.9 to 0.7; $P=0.41$).

Conclusion Esmolol reduces 28-day mortality, length of ICU stay and duration of mechanical ventilation in sepsis patients. Furthermore, esmolol improves oxygen metabolism, mitigates myocardial injury and decreases heart rate without significantly affecting hemodynamic parameters.

Trial registration This study was registered on the PROSPERO website (registration number: CRD42023484884).

Keywords Esmolol, Sepsis, Septic shock, Randomized controlled trials, Meta analysis

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Background

Sepsis is defined as a potentially fatal organ dysfunction caused by dysregulated host response to infection [1]. Studies have shown that the mortality of sepsis is as high as 50%. Sepsis is a threat to patient's health and generates enormous economic burden [2]. Due to excessive excitation of sympathetic nervous system [3], sepsis is often accompanied by tachycardia, arrhythmia and other cardiovascular events [4].

Beta-receptor blockers have been proposed to mitigate excessive sympathetic nervous system activity, thus reducing HR [5]. Esmolol, a β1-selective adrenergic receptor blocker, acts rapidly due to its short half-life and onset time. Previous studies have shown that esmolol attenuates inflammation and cell apoptosis in septic animal models, offering protection against sepsis-induced gastrointestinal mucosal damage [6, 7]. However, debate persists regarding the efficacy of esmolol in sepsis. The study by Morelli et al. indicated that esmolol decreased heart rate and 28-day mortality in patients with septic shock [8]. Some studies found that esmolol had no effect on 28-day mortality in sepsis patients [9–12]. Therefore, this meta-analysis seeks to assess the efficacy and safety of esmolol in sepsis treatment and provide evidence for its clinical application.

Materials and methods

This meta-analysis adhered to the PRISMA guidelines for systematic reviews and meta-analysis [13]. A detailed PRISMA checklist is included as an attachment. The meta-analysis protocol was registered prospectively with PROSPERO, ID CRD42023484884.

Search Strategy

Systematic searches were conducted in major English databases, including PubMed, Embase, Web of Science and Cochrane Library, up to March 1, 2024. Additionally, clinical trial registries such as clinicaltrials. gov and the Chinese Clinical Trial Registry were also searched. Relevant reviews and meta-analyses were manually screened for additional studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Study population: Adult patients diagnosed with sepsis or septic shock. Sepsis and septic shock were diagnosed according to Sepsis 1.0, Sepsis 2.0 or Sepsis 3.0 criteria [1, 14, 15]. (2) Intervention: Treatment with a combination of standard sepsis therapy and the infusion of esmolol. (3) Control: Standard sepsis therapy alone. (4) Outcome measures: The primary outcome was 28-day mortality. Secondary outcomes were length of intensive care unit (ICU) stay, duration of mechanical ventilation, dose of norepinephrine, cardiac troponin I levels (cTnI) levels, left ventricular ejection fraction (LVEF), heart rate (HR), central venous oxygen saturation ($ScvO_2$), mean arterial pressure (MAP) and central venous pressure (CVP). (5) Study design: Randomized controlled trials. Exclusion criteria were as follows: (1) Studies involving esmolol combined with other investigational drugs. (2) Duplicate publications. (3) Outcome measures cannot be extracted.

Data extraction and Quality Assessment

Two researchers (Wei and Bo) independently screened and extracted data according to predefined criteria. The Cochrane risk-of-bias tool was used for quality assessment [16]. Discrepancies were resolved by the corresponding author.

Statistical methods

Meta-analysis was performed using Review Manager 5.3 software. For dichotomous outcomes, relative risk (RR) and 95% confidence intervals (95% CI) were calculated. For continuous outcomes, standardized mean difference (SMD) and 95% CI were calculated. For continuous outcomes, standardized mean difference (SMD) and 95% CI were calculated. $P<0.05$ was considered statistically significant. If mean and standard deviation for continuous data could not be extracted directly, the method outlined in the BMC Medical Research Methodology was used to perform data conversion [17–20]. Heterogeneity was assessed using the I^2 and Q statistic. In the absence of significant heterogeneity ($I^2 \leq 50\%$ and $P \geq 0.1$), a fixed-effects model was applied. Conversely, significant heterogeneity between studies ($I^2 > 50\%$ or $P < 0.1$) warranted the use of a random-effects model. Publication bias was assessed using funnel plots if the number of included studies for a given outcome exceeded 10.

Results

Literature retrievals

There were 195 potential articles identified through the search of four English-language databases, and 14 additional articles identified by alternative methods, such as reviewing reference lists of existing meta-analyses. There were 106 duplicates removed. Then we excluded an additional 74 articles, which were either animal studies or review articles. Of the 29 articles reviewed in full text, 14 articles were excluded due to non-randomized controlled trials, repetitive publications, the presence of other intervention drug, and required outcome indicators could not be extracted. Thus, 15 articles were included in the final analysis, as depicted in Fig. 1 [8–12, 21–30].

Eleven studies were conducted in China [9–11, 21–25, 28–30], while four studies originated from other countries [8, 12, 26, 27], yielding data from 1100 patients, with 553 cases in the esmolol group and 547 cases in the control group. Five studies had duration of esmolol

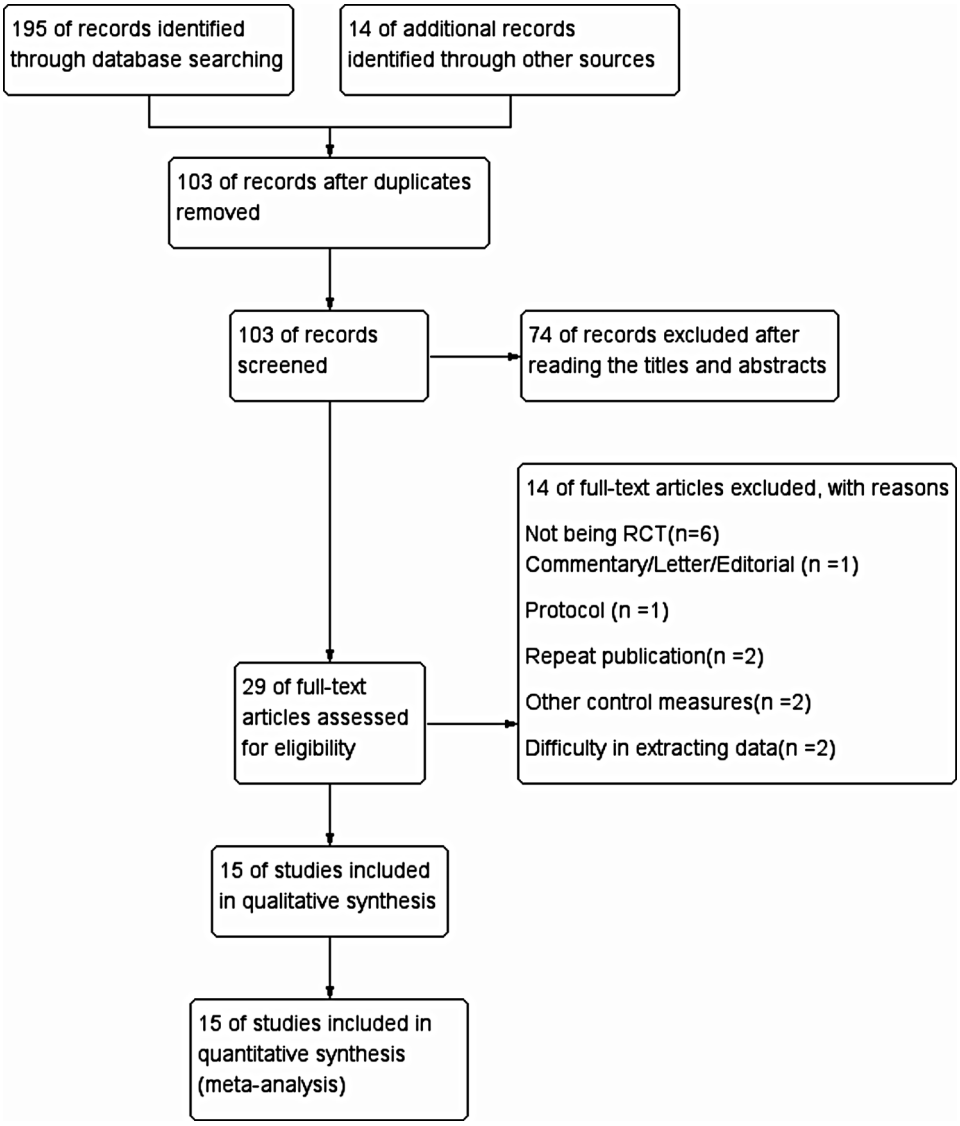
195 of records identified through database searching
14 of additional records identified through other sources
103 of records after duplicates removed
103 of records screened
74 of records excluded after reading the titles and abstracts
14 of full-text articles excluded, with reasons
Not being RCT(n=6)
Commentary/Letter/Editorial (n =1)
Protocol (n =1)
Repeat publication(n =2)
Other control measures(n =2)
Difficulty in extracting data(n =2)
29 of full-text articles assessed for eligibility
15 of studies included in qualitative synthesis
15 of studies included in quantitative synthesis (meta-analysis)

Fig. 1 Flow diagram of the publication selection

treatment for no more than 48 h [10, 21, 24, 27, 30], while the remaining 10 studies had durations exceeding 48 h [8, 9, 11, 12, 22, 23, 25, 26, 28, 29]. Five studies limited the maximum esmolol infusion rate to ≤0.2 mg/kg/min [10, 12, 21, 25, 26], two studies limited it to 0.3 mg/kg/min [11, 27], one study to 2000 mg/h [8], and the remaining seven studies adjusted the maximum esmolol infusion rate based on target HR without restriction [9, 22–24, 28–30]. General information extracted from relevant studies included the first author, publication year, country, number of patients, APACHE II score, intervention measures and outcomes (Table 1).

Risk of bias

Quality assessment was conducted for the 15 included articles. As shown in Fig. 2 and supplementary Fig. 1, all the included studies were considered to have low risk of bias in terms of random sequence generation (selection bias) and selective reporting (publication bias). Thirteen studies [8–12, 21–26, 28, 30] were assessed to have low risk of allocation concealment (selection bias), while two studies were considered high risk [27, 29]. Due to insufficient information, blinding assessment could not be evaluated in some studies. For participant and personnel blinding assessment, nine studies were considered high risk [8, 9, 11, 12, 23, 24, 26, 29, 30], two studies could not be evaluated due to lack of information [21, 28], and the remaining four studies were considered low risk [10, 22, 25, 27]. Four studies were considered high risk for incomplete outcome bias [9, 10, 24, 25], while the remaining eleven studies were assessed as low risk [8, 11, 12, 21–23, 26–30]. For other bias, 'Wang Shupeng 2017' was considered high risk due to potential data inaccuracies, while the others were assessed as low risk.

Table 1 Baseline characteristics of the included studies

Authors	Country	Comparisons	No. of patients (male%)	Age (years)	APACHE II score	Methods	Outcomes
Junyi Wang 2023[21]	China	esmolol	50(58)	69 (58,77.25) median (IQR)	27.5(21.75,33) median (IQR)	Given Esmolol at 24 h to maintain a heart rate between 80/min and 100/mi. The maximum maintenance dose can be increased to 0.2 mg/kg/min.	①②③④⑤⑥⑦⑧⑨⑩
		Control	50(56)	67.5(56.75,77) median (IQR)	29(26,32.25) median (IQR)	Basic treatment.	
Wang Shupeng 2017[10]	China	esmolol	30(60)	67.2 ± 12.5	18.4 ± 6.3	Continuous intravenous esmolol infusion for 24 hours, initial dose was 0.05 mg/kg/h to control HR below 95/min within 4 hours.	①④⑤
		Control	30(70)	62.5 ± 14.5	15.7 ± 6.3	Isotonic saline was given to the control group through an intravenous line at 3 mL/h for 24 hours.	
Liu Xinqiang 2015[22]	China	esmolol	24(46.7)	61.4 ± 6.9	20.75 ± 3.05	Micropump with dosage of esmolol 0.05 mg/kg/min to control HR below 100/min within 24 hours.	①②④⑤⑦⑧
		Control	24(43.3)	61.2 ± 6.4	21.21 ± 2.67	Basic treatment.	
Yang Shengqiang 2014[23]	China	esmolol	21(NA)	51.0 ± 22.6	20.1 ± 9.2	Micropump with dosage of esmolol 0.05 mg/kg/min to control HR below 100/min within 2 hours.	④⑤⑦⑧⑨
		Control	20(NA)	55.0 ± 25.4	21.3 ± 8.3	Basic treatment.	
Gao Xuehua 2015[9]	China	esmolol	33(51.5)	53.1 ± 11.4	17.1 ± 4.9	Pump esmolol continuously (HR 60–100/min).	①
		Control	29(44.8)	51.7 ± 10.0	18.3 ± 5.2	Basic treatment.	
Liu Huan 2019[11]	China	esmolol	50(58)	58 ± 15	18.8 ± 6.5	Continuous esmolol micropumps started at 25 mg/h. Maximum maintenance dose was 0.3 mg/kg/min. Continue for 7 days or until patient leaves ICU.	①②③④⑥
		Control	50(56)	57 ± 18	19.1 ± 7.5	Basic treatment.	
Zeng Wenxin 2016[24]	China	esmolol	37(NA)	56.0 ± 27.1	19.2 ± 8.7	Continuous infusion of esmolol (starting at a rate of 20 ug/kg/min) to achieve the target rate of 20 minutes (80–94/min), and continuous use for 48 hours to maintain the target heart rate.	②
		Control	34(NA)	58.2 ± 23.4	20.3 ± 7.2	Basic treatment.	
Yang Chun 2019[25]	China	esmolol	22(54.5)	56 ± 14	19 ± 5	The initial dose of esmolol is 0.05 mg/kg/min, adjusted according to heart rate, not exceeding 0.2 mg/kg/min, and the 24-hour heart rate is controlled between 75 and 94 beats per minute.	①④⑤⑦⑧⑨
		Control	22(40.9)	60 ± 11	18 ± 5	Continuously IV-pumped into the isotonic NaCl solution for 3 ml/h.	
Raouf Ramzy Gadallah 2020[26]	Egypt	esmolol	30(56.6)	58.3 ± 5.7	24.2 ± 5.4	esmolol intravenous infusion by starting dose of 0.05–0.2 mg/kg/min.	①②④⑤⑦⑧
		Control	30(76.6)	56.4 ± 4.8	23.5 ± 6.2	Basic treatment.	
Michael N. Cocchi 2022[27]	Israel	esmolol	18(56)	62(53,67) median (IQR)	NA	Continuous esmolol micropump commenced at 0.05 mg/kg/min to maintain HR 80 to 94/min for 24 hours.	②③⑥⑩
		Control	22(59)	64(59,71) median (IQR)	NA	Saline was given at the beginning of study interventions.	
Andrea Morelli 2013[8]	Italy	esmolol	77(70)	66(52,75) median (IQR)	NA	Continuous esmolol infusion commenced at 25 mg/h and adjusted dosage to reach the target heart rate between 80/min and 94/min within 12 hours.	①②
		Control	22(59)	64(59,71) median (IQR)	NA	Saline was given at the beginning of study interventions.	

Table 1 (continued)

Authors	Country	Comparisons	No. of patients (male%)	Age (years)	APACHE II score	Methods	Outcomes
Zhou Yihua 2019[28]	China	esmolol	67(NA)	41.6 ± 16.2	17.4 ± 6.8	The dosage of esmolol is adjusted according to heart rate, and the patient's heart rate is controlled between 60 and 100 beats per minute.	①②③⑩
		Control	67(NA)	41.9 ± 15.3	16.7 ± 7.9	Basic treatment.	
Zhou Jie 2019[29]	China	esmolol	32(50)	62.76 ± 9.49	NA	Esmolol was given an initial dose of 0.05 mg/kg/min, and the dose was adjusted according to changes in HR and blood pressure.	⑨⑩
		Control	32(56.3)	62.23 ± 9.77	NA	Basic treatment.	
LiSong Lin 2017[30]	China	esmolol	35(60)	53.12 ± 14.50	21.23 ± 8.29	The initial dose of esmolol is 50 mg/h, and the dose is adjusted according to the patient's blood pressure and heart rate. The course of treatment is 24 hours.	⑨
		Control	35(54.3)	52.87 ± 14.75	21.28 ± 8.2	Basic treatment.	
Bingul 2020[12]	Turk	esmolol	27(63.0)	46.6 ± 18.6	19.7 ± 6.1	Infuse esmolol to maintain a resting HR between 85 and 95 bpm for 4 days. The maximum maintenance dose can be increased to 100 mg/kg/min.	①③④⑤⑥⑦
		Control	25(68)	55.5 ± 15.6	20.5 ± 6.4	Basic treatment.	

Values are reported as mean ± SD unless otherwise indicated, APACHE II acute physiology and chronic health evaluation II, NA not available, ① 28-day mortality, ② length of ICU stay, ③ mechanical ventilation time, ④ heart rate, ⑤ mean arterial pressure, ⑥ norepinephrine dosage, ⑦ central venous pressure, ⑧ central venous oxygen saturation, ⑨ cardiac troponin I, ⑩ left ventricular ejection fraction

Primary outcome

Ten studies reported 28-day mortality [8–12, 21, 22, 25, 26, 28]. Compared with the control group, esmolol significantly reduced 28-day mortality (RR, 0.69; 95% CI, 0.60 to 0.81; $P<0.0001$) (Fig. 3). Furthermore, esmolol still reduced 28-day mortality (RR, 0.69; 95% CI, 0.59 to 0.80; $P<0.0001$) when the study [10] being excluded due to the different usage of esmolol from current clinical guideline (Supplementary Fig. 2).

Based on the country where the trial conducted, the included studies were divided into two subgroups: China group and other countries group. There were 7 studies from China [9–11, 21, 22, 25, 28] and 3 studies from other countries [8, 12, 26]. It was showed that whether the studies were conducted in China (RR, 0.76; 95% CI, 0.62 to 0.93; $P=0.008$) or other countries (RR, 0.63; 95% CI, 0.51 to 0.78; $P<0.0001$), esmolol could reduce the 28-day mortality of septic patients (Supplementary Fig. 3).

Based on doses of esmolol use in septic patients, the studies were divided into three subgroups: esmolol infusion with the rate of ≤0.2 mg/kg/min [10, 12, 21, 25, 26], >0.2 mg/kg/min [8, 11], and unrestricted rate [9, 22, 28]. It was showed that esmolol could reduce the 28-day mortality of septic patients (≤0.2 mg/kg/min, RR, 0.70; 95% CI, 0.53 to 0.92; $P=0.01$; >0.2 mg/kg/min, RR, 0.72; 95% CI, 0.59 to 0.87; $P=0.0006$; Unrestricted rate, RR, 0.53; 95% CI, 0.33 to 0.85; $P=0.009$) (Supplementary Fig. 4).

Based on the duration of esmolol infusion, the studies were divided into three subgroups: duration of esmolol continuous infusion ≤ 48 h [10, 21], 49 h to 96 h [12, 22, 25, 28] and >96 h [8, 9, 11, 26]. It was showed that duration of esmolol continuous infusion ≤ 48 h had no effect on the 28-day mortality of septic patients (RR, 0.69; 95% CI, 0.46 to 1.04; $P=0.07$), while when duration of esmolol continuous infusion > 48 h, esmolol significantly reduced 28-day mortality (49 h to 96 h: RR, 0.57; 95% CI, 0.38 to 0.86; $P=0.007$; >96 h, RR, 0.73; 95% CI, 0.85 to 0.91; $P=0.007$) (Supplementary Fig. 5).

Secondary outcomes

Hemodynamic parameters

This meta-analysis included 9 studies reporting HR [10–12, 21–26], 7 studies reporting CVP [12, 21–26], 8 studies reporting MAP [10, 12, 21–26], 5 studies reporting dosage of norepinephrine [11, 12, 21, 24, 27], and 4 studies reporting LVEF (Table 2) [21, 25, 28, 29]. It was showed that esmolol significantly reduced the HR of septic patients (SMD, -1.15; 95% CI, -1.34 to -0.96; $P<0.0001$) (Supplementary Fig. 6). While, esmolol application had no effect on CVP (SMD, 0.16; 95% CI, -0.04 to 0.35; $P=0.11$; Supplementary Fig. 7), MAP (SMD, 0.17; 95% CI, -0.07 to 0.4; $P=0.16$; Supplementary Fig. 8), LVEF (SMD, -0.17; 95% CI, -0.39 to 0.05; $P=0.12$; Supplementary Fig. 9) and dosage of norepinephrine (SMD, 0.08; 95% CI, -0.13 to 0.29; $P=0.46$; Supplementary Fig. 10).

Myocardial injury

Five studies reported changes in cTnI levels [21, 23, 25, 29, 30], showing that esmolol could reduce the cardiac

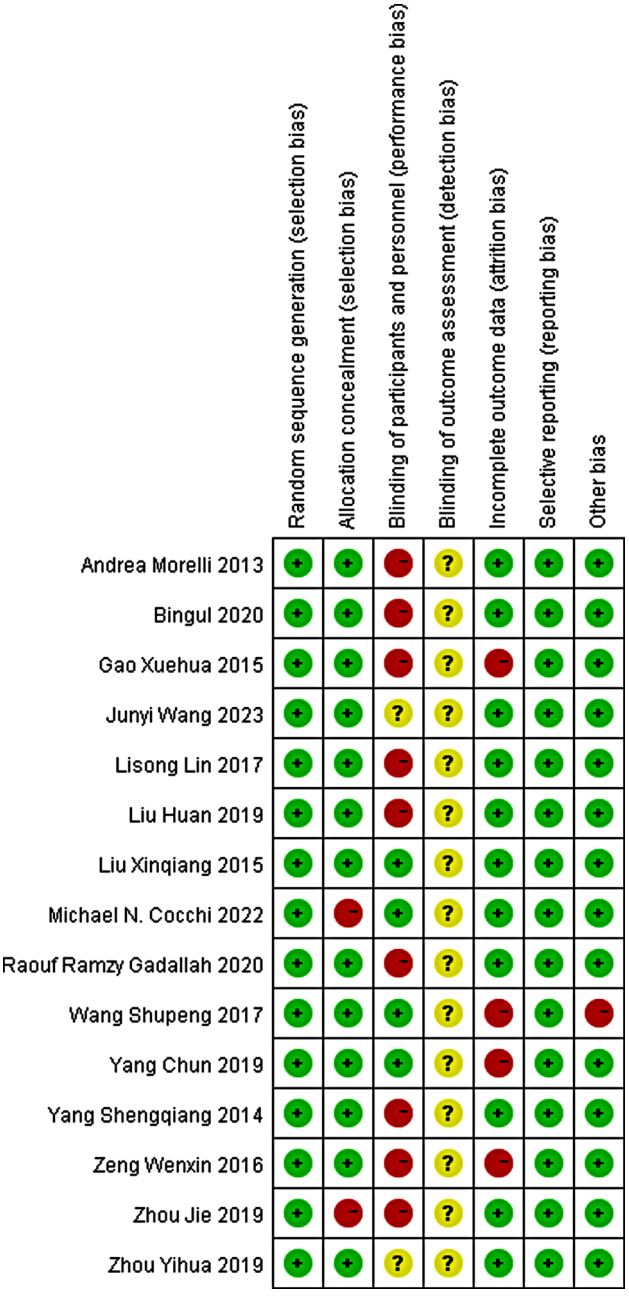

Fig. 2 Risk of bias summary for the included studies

troponin I of septic patients (SMD, -0.88; 95% CI, -1.13 to -0.64; *P*<0.0001; Fig. 4).

$ScvO_2$

Six studies reported $ScvO_2$ [11, 12, 22–24, 26], showing that esmolol could increase the central venous oxygen saturation of septic patients (SMD, 0.66; 95% CI, 0.44 to 0.88; *P*<0.0001; Fig. 5).

Mechanical ventilation time and length of ICU stay

Five studies reported mechanical ventilation time [11, 12, 21, 27, 28], and seven articles reported length of ICU stay [8, 11, 21, 22, 26–28]. It showed that esmolol significantly reduced the mechanical ventilation time (SMD, -0.28; 95% CI, -0.48 to -0.09; *P*=0.004) and length of ICU stay (SMD, -0.46; 95% CI, -0.62 to -0.3; *P*<0.0001) of septic patients (Fig. 6).

Heterogeneity analysis

For 28-day mortality, MAP and LVEF, the heterogeneities were not statistically significant ($I^2 \leq 50\%$ and $P \geq 0.1$). While for the remaining outcomes, the heterogeneities were significant ($I^2 > 50\%$ or $P < 0.1$).

Publication bias

Among the outcome indicators of this study, only the primary outcome indicators were included in 10 articles [8–12, 21, 22, 25, 26, 28]. Publication bias was assessed using funnel plots. It showed that there was minimal publication bias between the included studies (Supplementary Fig. 11).

Discussion

This study demonstrates that esmolol reduces 28-day mortality, shortens the duration of mechanical ventilation and the length of ICU stay, and decreases oxygen consumption, cardiac injury and heart rate without compromising hemodynamics in patients with sepsis. Our results align with several prior meta-analyses [31–36], yet our study encompasses a broader literature review and excludes studies co-administering positive inotropes such as milrinone [37], thereby minimizing the confounding effects of concurrent medications.

Esmolol exerts protective effects in septic patients, such as reducing mortality and shortening length of ICU stay. The reasons may be as follows: (1) Sympathetic nervous system is overactivated during sepsis. Esmolol, as a commonly used β-adrenergic receptor blocker, can inhibit excessive activation of sympathetic nervous system, reduce HR and decrease myocardial oxygen consumption [12]. (2) Multiple studies have shown that esmolol can inhibit the excessive activation of inflammatory response and the release of inflammatory factors [38, 39]. Excessive activation of inflammatory response may lead to septic cardiomyopathy [40–42]. (3) Animal experiments have shown that esmolol can regulate the function of the immune system and alleviate the immune imbalance in septic patients [43, 44].

In order to find out the appropriate dose and infusion time of esmolol for sepsis, subgroup analysis was conducted. Interestingly, we found that esmolol still reduced the 28-day mortality in the septic patients even using a relevant low dose (less than 0.2 mg/kg/min). However,

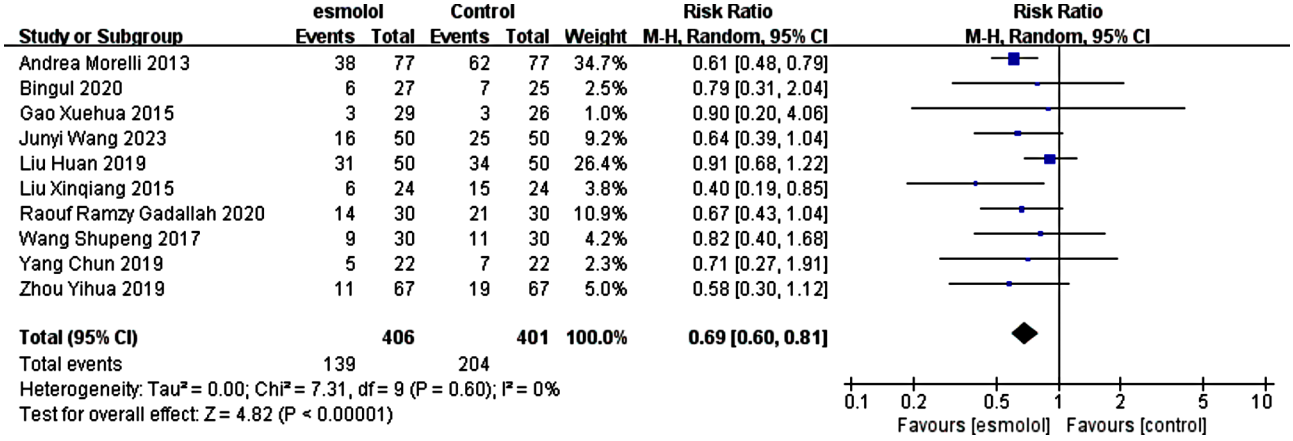

Fig. 3 A forest plot of 28-day mortality between the esmolol and control groups

Table 2 Meta-analysis of the hemodynamic effects of esmolol versus control in septic patients

Outcomes	Number of studies	Number of cases		Effect model	SMD	95%CI	*P*
		esmolol	control				
HR	9 [10–12, 21–26]	291	288	Fixed	-1.15	-1.34 ~ 0.96	<0.0001
CVP	7 [12, 21–26]	211	208	Fixed	0.16	-0.04 ~ 0.35	0.11
MAP	8 [10, 12, 21–26]	241	238	Random	0.17	-0.07 ~ 0.4	0.16
LVEF	4 [21, 25, 28, 29]	226	226	Random	-0.17	-0.39 ~ 0.05	0.12
Norepinephrine dosage	5 [11, 12, 21, 24, 27]	237	239	Fixed	0.08	-0.13 ~ 0.29	0.46

HR heart rate, CVP central venous pressure, MAP mean arterial pressure, LVEF left ventricular ejection fraction, SMD standard mean difference, 95%CI 95% confidence interval

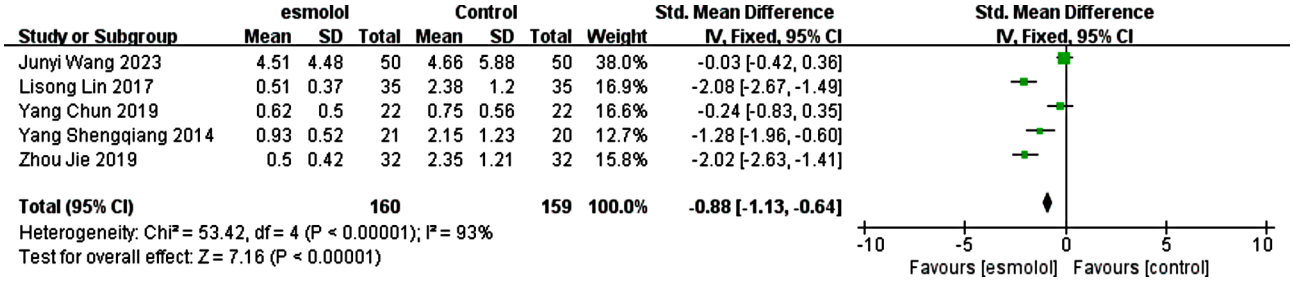
esmolol
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Junyi Wang 2023 4.51 4.48 50 4.66 5.88 50 38.0% -0.03 [-0.42, 0.36]
Lisong Lin 2017 0.51 0.37 35 2.38 1.2 35 16.9% -2.08 [-2.67, -1.49]
Yang Chun 2019 0.62 0.5 22 0.75 0.56 22 16.6% -0.24 [-0.83, 0.35]
Yang Shengqiang 2014 0.93 0.52 21 2.15 1.23 20 12.7% -1.28 [-1.96, -0.60]
Zhou Jie 2019 0.5 0.42 32 2.35 1.21 32 15.8% -2.02 [-2.63, -1.41]
Total (95% CI) 160 159 100.0% -0.88 [-1.13, -0.64]
Heterogeneity: Chi² = 53.42, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 7.16 (P < 0.00001)
-10 -5 0 5 10
Favours [esmolol] Favours [control]

Fig. 4 A forest plot of cardiac troponin I levels between the esmolol and control groups

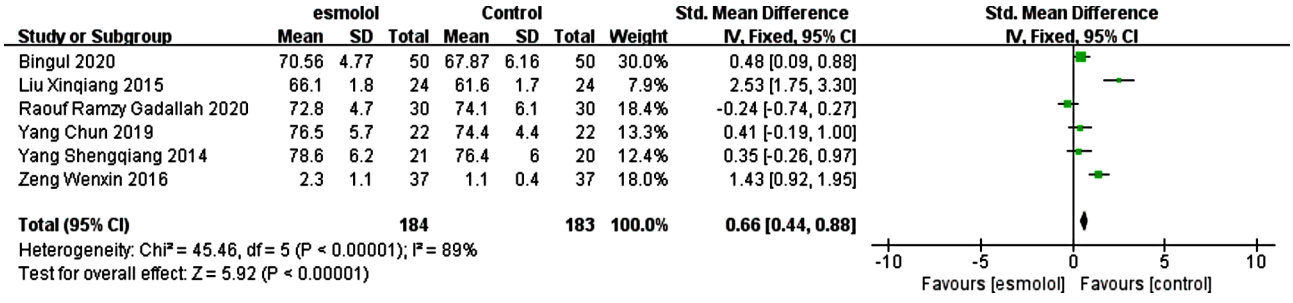
esmolol
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Bingul 2020 70.56 4.77 50 67.87 6.16 50 30.0% 0.48 [0.09, 0.88]
Liu Xinqiang 2015 66.1 1.8 24 61.6 1.7 24 7.9% 2.53 [1.75, 3.30]
Raouf Ramzy Gadallah 2020 72.8 4.7 30 74.1 6.1 30 18.4% -0.24 [-0.74, 0.27]
Yang Chun 2019 76.5 5.7 22 74.4 4.4 22 13.3% 0.41 [-0.19, 1.00]
Yang Shengqiang 2014 78.6 6.2 21 76.4 6 20 12.4% 0.35 [-0.26, 0.97]
Zeng Wenxin 2016 2.3 1.1 37 1.1 0.4 37 18.0% 1.43 [0.92, 1.95]
Total (95% CI) 184 183 100.0% 0.66 [0.44, 0.88]
Heterogeneity: Chi² = 45.46, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 5.92 (P < 0.00001)
-10 -5 0 5 10
Favours [esmolol] Favours [control]

Fig. 5 A forest plot of central venous oxygen saturation levels between the esmolol and control groups

esmolol did not reduce the 28-day mortality of septic patients when the duration of esmolol infusion was ≤48 h. This may provide some reference for optimizing treatment strategy of esmolol in septic patients.

As we know, esmolol is a negative inotropic agent. Therefore, our study assessed the safety of esmolol in sepsis patients. The results showed that esmolol did not increase noradrenaline dosage, decrease mean arterial pressure or left ventricular ejection fraction (LVEF).

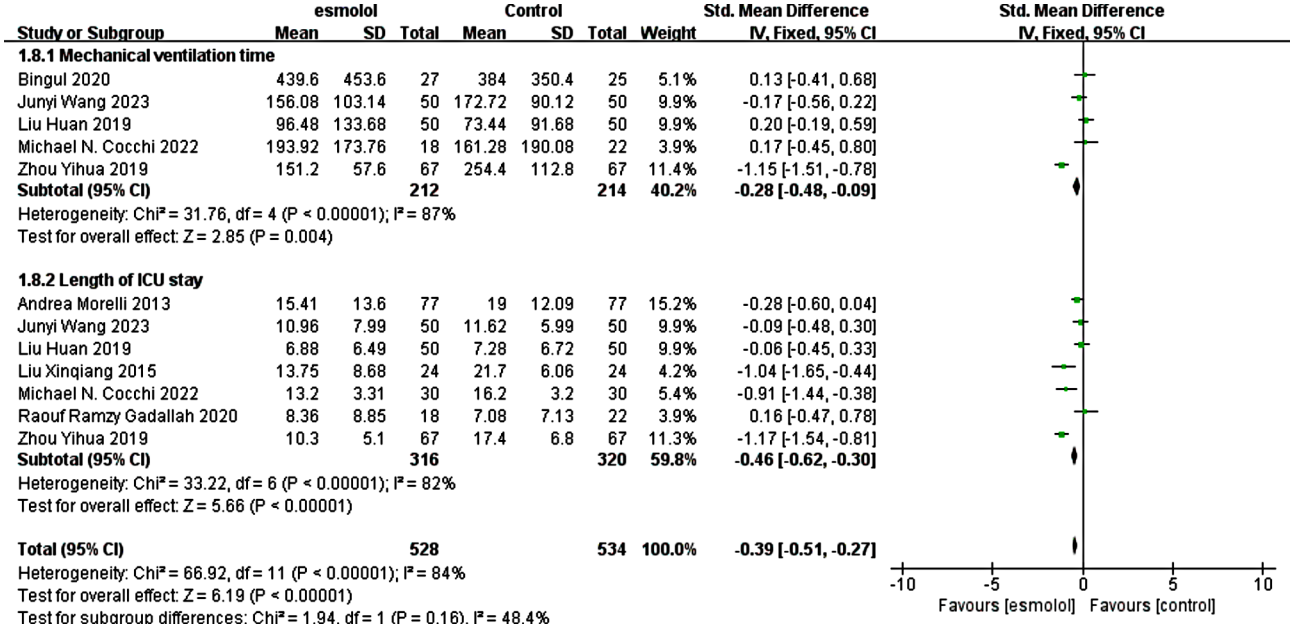

Fig. 6 A forest plot of the consumption of medical resources between the esmolol and control groups

There are several reasons why esmolol has no significant negative effect on hemodynamic parameters. Firstly, esmolol used in small dosage in most of the included studies. Secondly, persistent tachycardia increases myocardial oxygen consumption and shortens left ventricular diastolic time thereby decrease coronary artery perfusion and cardiac output [45], while control of heart rate by esmolol prolongs left ventricular diastole, increases left ventricular blood volume and LVEF [46], increases coronary artery perfusion and improves stroke volume. In other words, the benefits of esmolol in controlling HR offset the harms of its negative inotropic effects. Finally, previous study has shown that esmolol can improve left ventricular compliance and increase blood volume in septic patients [47]. As esmolol reduces ventricular rate, improves ventricular compliance and increases LVEF and effective circulating blood volume [46, 47], it may improve oxygen metabolism for sepsis patients as previous study has indicated [48]. This may be the reason why our study found that esmolol increased $ScvO_2$ in septic patients. In addition, the meta-analysis showed that esmolol could improve cardiac injury in sepsis. Some studies have confirmed that esmolol decreases peak troponin levels and improves cardiac function in patients after cardiac surgery [49, 50].

Finally, it must be acknowledged that our study also has some limitations. Firstly, for length of ICU stay, mechanical ventilation time, norepinephrine dosage and cTnI, some of these continuous data were obtained via conversion, which may impact the pooled estimates. Secondly, the potential influence of prior β-blocker exposure was not clarified clearly. Thirdly, the variability in reporting NE salt formulations in the included studies, which complicated the assessment of severity and prognosis of critical illness [51–54]. A recent position statement strongly recommended the adoption of a standardized NE formulation globally [55]. Unfortunately, the studies did not report the specific NE salt formulations, precluding differentiation among tartrate, bitartrate or hydrochloride forms in our analysis. Finally, our study indicated that continuous use of esmolol less than 48 h failed to lower 28-day mortality in sepsis patients. However, the analysis was constrained by a limited sample size, including only 160 patients from two studies [10, 21]. Therefore, the optimal dosage and duration of esmolol in sepsis still need to be investigated.

Conclusion

Esmolol significantly reduces the 28-day mortality and the utilization of critical medical resources in ICU in patients with sepsis. Esmolol also improves oxygen metabolism, alleviates myocardial injury and decreases HR, but has no negative influence on hemodynamic parameters in patients with sepsis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02714-3.

Supplementary Material 1: The supplementary material contains search strategies, list of abbreviations and supplementary figures.

Supplementary Material 2

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None.

Author contributions
Y. W. and F. B. are the guarantors of this work and as such have full access to all data in the study and take responsibility for the integrity of data and the accuracy of data analysis. Y. W. and F. B. are equally responsible for the conception of the study, collection and analysis of data, interpretation of data, writing of the draft manuscript, and critical revision of the manuscript. J. W. substantially contributed to the collection of data. X. L. , J. F. and Y. Q. substantially contributed to the analysis and interpretation of data. X. L. , H. B. and D. H. supervised the drafting and revision of the manuscript. All authors approved the submission of the final manuscript.

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Data availability
Data of the studies analysed are already available in publications.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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